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REVIEWS

Circadian Rhythms: Physiological and Pathophysiological Aspects

S. M. Drogovoz,[1] N. M. Seredyns'ka,[2] A. L. Shtroblya,[3] V. D. Luk'yanchyuk,[5] R. V. Lutsenko,[4] T. V. Krutskykh,[1] A. L. Panfilova,[1] L. V. Derymedvid',[1] and M. V. Shtroblya[3]

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Physiological and pathophysiological aspects of the functioning of the cerebral system (hypothalamus and cerebral epiphysis) providing the circadian rhythm in humans are described with special attention to the involvement of disorders in this system in the pathogenesis of some neurodegenerative diseases and epilepsy.

Keywords: circadian rhythm, hypothalamus, cerebral epiphysis (pineal gland), melatonin, oxidatin stress, neurodegenerative diseases, epilepthy.

The circadian rhythm in humans, as well as that in other animals, is an important factor in physiology. In this review, we consider physiological and pathophysiological aspects in humans only. Organization of physiological functions in a rhythmic/cyclic mode is crucial for homeostasis as it allows an organism to adapt to the periodical processes in its environment. A classic example of this adaptation is a systemic sleep/wake cycle controlled by the circadian rhythm [1]. Subordination of this rhythm leads to periodical changes in the characteristics of physiological functions and behavior through a ~24-h-long cycle (according to changes in the intensity of natural illumination) [2]. There is hardly an organ in the human body that is independent of this "24-h" cycle; disorganization of this circadian rhythm can lead to sleep disruption and some manifestations accompanying other pathologies. [3, 4]. According to many studies, the circadian rhythm is extremely important for adequate (normal) functioning of the neural system, and its disruption inhibits and disorganizes this functioning [5].

The hypothalamus and pineal gland (cerebral epiphysis) complex are general regulators of the circadian rhythms in the functions of visceral organs and systems; the hormone melatonin produced by the epiphysis plays the role of the main biochemical mediator in this regulation [6].

In this review, we concentrate strictly on physiological and pathophysiological aspects affecting circadian rhythms. Such groups of issues such as the process of the production of melatonin by the epiphyseal cell components and the structural/functional relations between the epiphyseal/hypothalamic complex and the visual sensory system (the main factor providing synchronization of the epiphyseal system with cyclic changes in the environment), i.e., issues that are very important in themselves, are considered to a limited extent.

In humans, the central pacemakers of the circadian system are the suprachiasmatic nuclei (SCN) of the hypothalamus. The latter is the main regulator of a wide spectrum of behavioral and physiological processes, including the sleep-wake cycle, cardiovascular physiology, thermoregulation, human spatial movements, many endocrine processes, etc. [7]. The inner "clock" of the SCN

[1] National University of Pharmacy, Ministry of Health of Ukraine, Kharkiv, Ukraine.
[2] Institute of Pharmacology and Toxicology, National Academy of Medical Sciences of Ukraine, Kyiv, Ukraine.
[3] Uzhhorod National University, Uzhhorod, Ukraine.
[4] Poltava State Medical University, Ministry of Health of Ukraine, Poltava, Ukraine.
[5] Pylyp Orlyk International Classic University, Mykolaiv, Ukraine.
Correspondence should be addressed to N. M. Seredyns'ka (e-mail: nvivalna@gmail.com).

is controlled by both genes and environmental factors that synchronize the 24-h cycle [8]. If there is a desynchronization of this rhythm (i.e., under conditions of shift work, the so-called jet lag, aging, some mental disorders, blindness, etc.), the organism stops being harmonized with astronomic time, i.e., with the natural clock.

Thus, circadian oscillations of neural functions play a pivotal role in the cyclical regulation of the processes of the human organism. Daily fluctuations in the tonus of the autonomous (vegetative) nervous system (ANS) are strongly correlated with the light/dark and sleep/arousal cycles. A sympathetic part of the ANS is subjected to tonic descending up-regulation during a diurnal period, whilst a parasympathetic part of this system is mostly activated during nocturnal sleep. These biorhythms are regulated via the pineal gland by modulation of the production of the aforementioned neurotropic hormone, melatonin [9].

Any malfunction of the nervous system affects biorhythms. The respective shifts induce dysfunction of central and peripheral nervous systems, as well as cognitive disorders. There are two sides to chronopathology for the nervous system: chronobiological failure can be caused by previous organic and functional brain pathology, and/or neural disorders can evolve secondary negative changes due to biorhythm disruption [9]. For example, dysfunction of the pineal gland and SCN, as well as a melatonin deficiency, can lead to depression, though there is a strong possible role of disruption of other brain functions such as higher-order cognitive and emotion/motivational behavior.

Synthesis and secretion of melatonin is controlled by the circadian cyclical activity of the SCN [10]. This hormone, known as N-acethyl-5-metoxytryptamin, was first discovered sixty years ago and is a multifunctional substance majorly produced by the pineal gland "in response to dusk" [11]. Its secretion is defined by the circadian rhythm; the concentration of this hormone in humans is approximately ten-fold higher at night than under conditions of daylight (growing at 9 p.m. if the duration of night/daylight is 12 hours each). The secretion peaks within the night hours and lowers in the morning [12]. Protein receptors sensitive to melatonin are expressed in the SCN; this forms a regulation loop impacting all levels of the circadian network and allows this hormone to influence rhythms throughout the 24-h day [13]. Melatonin regulates physiological circadian rhythms, in particular the sleep-arousal cycle, neuroendocrine rhythms, and cycles of body temperature shifts, via the action of MT1 and MT2 receptors. The former receptors are widely expressed in the tuberal part of the anterior pituitary and hypothalamus (an anatomic correlate of the "circadian clock"), and also in the cerebral cortex, thalamus, *substantia nigra*, hippocampus, cerebellum, and cornea [14]. The MT2 receptors are expressed predominantly in the retina, hippocampus, brain cortex, and cerebellum [15]. Melatonin receptors have been found in peripheral tissues such as the heart, adrenal glands, kidneys, lungs, liver, bladder, small intestine, womb, mammary glands, prostate, and skin [16]. In addition, nowadays the unique properties of melatonin have been confirmed. This hormone stimulates the production of cytokines, in particular interleukins (IL-2, IL-6, and IL-12) [17] and enhances the immune response of T-helpers [18]. The antioxidant effect of melatonin contributes to its immunostimulating effects [17] as well as to the reduction of inflammatory reactions [19]. Melatonin, as an internal time regulator in a complex network of the body's circadian clock (due to its daily rhythm of secretion), amplifies time signals to numerous target tissues that have melatonin receptors. In addition to the well-known and already listed effects of melatonin and its participation in the regulation of the sleep-wake cycle, it is perceived as an endogenous synchronizer and chronobiotic molecule in the regulation of the synchronization of the central biological clock located in the SCN of the hypothalamus [12].

Melatonin is synthesized and secreted mainly by pinealocytes of the pineal gland at night under normal conditions of alternations of light and darkness. It may be stated that the main physiological function of melatonin is to transmit information to the body about the daily external cycle of light and darkness regulated by the length of the night. The daily secretion of melatonin is a very strong chemical "night signal"; it is used as a pharmacological agent for corrections of circadian rhythm disorders. There is ample evidence that melatonin stabilizes and enhances circadian rhythms, especially sleep/arousal ones [20–22]. The circadian organization of the functions of other physiological systems and organs also depends on the intensity of the melatonin signal. This applies, for example, to the immune system and antioxidant protection, hemostasis, and glucose level regulation. Up to now, the difference between the physiological

and pharmacological effects of melatonin has not been studied in sufficient detail, but it has been established that its significance is based mainly on the size of the dose and not on the duration of action of this hormone [10].

The intensity of melatonin synthesis decreases with age and in some neurodegenerative diseases, indicating that a disruption of the synthesis of this hormone in the body can cause the development and/or progression of some diseases. In addition, melatonin has been shown to possess clear neuroprotective, antioxidant, and anti-inflammatory effects [1, 23, 24]. Melatonin, in general, stimulates the CNS functioning, which leads in particular to increased secretion of norepinephrine [25]. Melatonin levels usually decrease in the elderly; such a shift can contribute to the development of neurodegenerative diseases in this category of people [26]. It was shown that the latter pathologies manifest common pathophysiological signs including disruption of the circadian rhythms, abnormally increased intensity of oxidative stress, neuroinflammation, loss of neurons, and mitochondrial dysfunction [10, 27, 28]. Thus, firstly, the system of regulation of melatonin secretion in the body is complex and is implemented by central and vegetative endogenous ways. The role of melatonin in the regulation of body biorhythms is crucial due to the unique adaptation-related properties of this hormone. There are many pathophysiological situations in the nervous system in which the secretion of melatonin can be disturbed and have the potential to increase susceptibility to neurological diseases, induce rises in the severity of their symptoms, and significantly change the course of the disease. Disruption of melatonin production leads to the development of a desynchronization syndrome and to the formation of a state of desynchronization, which can lead to the initiation and/or strengthening of various other pathologies. Secondly, since melatonin receptors are very widely distributed and common in the body, the intended therapeutic indications for the use of this compound are rather numerous [29]. Changes in the level and rhythm of melatonin secretion are found in various pathological conditions of the nervous system. The listed pathological conditions are manifested as sleep disorders, impaired cognitive functions, depression, and neuropathies [30].

Today, neurodegenerative diseases are the second leading cause of death in the world; they are characterized by progressing disorders of the motor and/or mental functions and structural changes in the central and peripheral nervous systems [31]. Therefore, the prevention and treatment of these diseases is an important and urgent healthcare problem. Melatonin performs a number of different physiological functions in the CNS, including regulation of the circadian rhythms and inhibition of lipid peroxidation, which helps to suppress the neuroinflammatory processes. Thus, this agent affects important pathophysiological phenomena in the body by performing a wide range of neuroprotective functions within the nervous system; this is why therapeutic applications of melatonin are rather diverse [27, 32, 33]. It should be mentioned that the levels of melatonin in patients suffering from neurodegenerative diseases are, as a rule, strongly reduced [34–36]. Considering this, we have been able to better understand the therapeutic potential of melatonin in the case of its use for the treatment of various neurodegenerative diseases. It is known that melatonin concentrations in blood serum and cerebrospinal fluid in patients with bronchial asthma are lower than the norm [37]. In addition, melatonin administration was shown to reduce disturbances of the circadian rhythm and improve cognitive functions in patients with Alzheimer's disease (AD) [38]. Another dangerous and widespread disease, Parkinson's disease (PD) is a chronic neurodegenerative pathology, the main mechanism of which is destruction of the cerebral dopaminergic system and depletion of dopamine [39]. As was reported, melatonin noticeably inhibits oxidative stress and apoptosis in PD, and this is definitely associated with the preservation of the number of dopaminergic neurons [40]. Other publications have also reported that melatonin reduces the intensity of oxidative stress, moderates mitochondrial dysfunction, and ameliorates behavioral disorders by increasing dopamine levels [41, 42]. It has been proven that the introduction of melatonin leads to increases in the concentration of acetylcholine, norepinephrine, and DOPA in the hippocampus [32, 43]. In addition, melatonin administrations were reported to effectively reduce the levels of oxidative stress markers (such as thiobarbituric acid) and to increase concentrations of antioxidant factors, including superoxide dismutase and glutathione (SOD and GSH respectively), thus providing an increase in the total antioxidant capacity [43, 44].

Epilepsy is a chronic neurological disease manifested primarily in the generation of seizures

due to strong pathological activation of various neural mechanisms. In many cases, an important cause of such changes is an abnormal intensification of oxidative stress. Within the last three to four decades, a possible causal connection between epilepsy and the state of the melatonin system has been researched. Studies on experimental animal models showed the existence of a clear correlation between the level of melatonin and the intensity of epileptogenesis and confirmed the hypothesis that this hormone can provide a significant antiseizure effect. Today, the existence of a possible correlation between the concentration of melatonin and the course of the disease in patients with epilepsy is being intensively discussed, and the possibilities for the application of melatonin in antiepileptic therapy are being studied [45].

Normal levels of neurohormones, in particular melatonin, are especially important for adequate functioning of the cardiovascular system; their levels exhibit diurnal fluctuations and play a role in the synchronization of molecular circadian clocks in peripheral tissues and CNS. Today, more and more evidence has been obtained indicating that changes in the rhythm of melatonin secretion and its concentration in the blood play a decisive role in disorders of some cardiovascular functions, including daily fluctuations of blood pressure [46]. From the point of view of systemic neurophysiology, melatonin is an immunochronobiotic.

The state of the melatonin system is noticeably affected by aging. Melatonin is a powerful antioxidant that supports the redox balance and prevents the excessive formation of free radicals, this agent is a regulator of metabolic sensitivity and an antagonist of insulin resistance. Aging processes and the development of age-related diseases are closely related to the loss of melatonin secretion and changes in the amplitude of the circadian rhythm. Therefore, the correlation between melatonin levels and dynamic properties of aging processes deserves special attention [47].

It is known that significant changes occur with aging in the function of the pineal gland; in a parallel manner, the secretion of melatonin (one of the main physiological nootropic hormones) decreases; in addition, the melatonin deficiency is accompanied by increased lipid peroxidation, neurodegeneration, immune deficiency, and sleep deterioration [48]. In a number of studies, it was found that the administration of exogenous melatonin provides analgesic and neuroprotective effects in chronic pain [49]. Disruption of the rhythms of melatonin production was found in AD, which may be an important cause of the desynchronosis in this disease [50]. Understanding the relationship between AD and disruption of the circadian rhythms of melatonin production may make possible early recognition of the possibility of dementia development and improve targeted approaches to the therapy of this disease. In particular, the inclusion of melatonin, which provides sleep improvement, in this therapy, may be useful in preventing the progression of the development of this disease [51].

In patients with schizophrenia, the intensity of depressive symptoms usually increases in the evening. This indicates that there is a close connection between the circadian biorhythms and the development of anxiety states. In the clinical dynamics of schizophrenia, clear daily, monthly, and seasonal (circannual) rhythms are observed. It is quite obvious that circannual rhythms are largely derived from circadian ones (corresponding to the daylight duration) and apply, in any case, to both the temperate and high latitudes of the globe. In particular, it is known that pronounced depression in schizophrenia manifests itself mainly in winter, while hypomania is usually intensified in spring and summer [52]. The frequency and time of occurrence of strokes also depend on circadian and higher-order rhythms. Pathological paroxysmal states of patients are associated with sleep phases: strokes and autonomic-vascular crises mainly occur during a fast phase of sleep, while generalized epileptic seizures are more frequent within slow phases. Epilepsy and, in particular, epileptic convulsive attacks, are a vivid example of a pathology associated with a violation of the biorhythms. The maximum frequency of such attacks is observed within periods of low insolation, namely in the autumn and winter periods. Epilepsy attacks are more than twice as rare from March to August than from October to February [53].

A fairly close causal relationship between circadian rhythms and mood regulation has been established. The presence of such a connection with mood disorders is convincingly confirmed by the facts of the antidepressant effectiveness of innovative pharmacological treatment methods aimed at resynchronizing endogenous rhythms in patients with depression [54]. Thus, the effectiveness of mood stabilizers can be partly explained by their influence on the regulation of circadian rhythms [55].

Thus, an adequate and comprehensive assessment of circadian rhythms is useful and highly desirable for both the diagnostics and treatment of patients with disorders of a number of the nervous system functions. Abnormal changes in the circadian rhythms indicate their strong connection with the development of neurodegenerative diseases and mental disorders [53]. Melatonin is a natural antioxidant with circadian secretion; its depletion or absence clearly leads to significant damage to the functions and structure of various cells, including CNS neurons. Therefore, the disruption of the circadian rhythm with the subsequent intensification of oxidative stress and the increase of inflammatory processes may be the most important pathophysiological factor causing CNS diseases and affecting their development [27, 56].

The complex nature of the human circadian system and the impact of its functioning on sleep and health in general confirm the need for a careful assessment of the circadian rhythm in the clinical treatment of neurological diseases. The ability to adequately assess the circadian rhythms and the degree of their disruption can help significantly in the treatment of these disorders. Advances in modern neurophysiology, neurochronopathology, and chronopharmacology open up opportunities to enhance the therapeutic effect of pharmacological agents and reduce their side effects.

This paper is a review and, thus, the correspondence of the study to the existing ethical standards does not need special confirmation. In all mentioned studies involving human subjects, the existing international ethical norms have been strictly observed.

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